

Influence of selected donor characteristics on the troponin I levels after heart transplantation: a single centre experience

Wpływ wybranych czynników związanych z dawcą serca na wartości poziomów troponiny I po przeszczepieniu serca – opis na podstawie materiału własnego

Karol Wierzbicki¹, Dorota Sobczyk¹, Irena Milaniak¹, Maciej Bochenek¹, Bogusław Kapelak¹, Rafał Drwiła¹, Krzysztof Wróbel¹, Krzysztof Bartuś¹, Dorota Ciotczyk-Wierzbicka², Piotr Przybyłowski¹, Jerzy Sadowski¹

¹Department of Cardiovascular Surgery and Transplantology, Jagiellonian University Medical College, John Paul II Hospital, Krakow, Poland

²Chair of Medical Biochemistry Jagiellonian University Medical College, Krakow, Poland

Kardiochirurgia i Torakochirurgia Polska 2011; 4: 516–520

Abstract

Introduction: The selected factors connected with the heart donor may influence the extent of the harvested heart injury.

Aim of the study: To assess the influence of selected factors connected with heart donor on troponin I levels in the perioperative period (from day 0 to day 3).

Material and methods: Retrospective analysis included 30 patients (4 females, 26 males) aged 22 to 62 years, average 48.5 ± 11.00. The study group consisted of the patients whose hearts were harvested according to the same scheme. In all patients, troponin I levels were measured on the consecutive days after HTX.

The following features were analyzed: donor's age, cause of donor's death, vasopressants' use and total ischemic time (TIT). Troponin I levels were measured by one step immuno-enzymatic test (normal values up to 0.1 ng/ml).

Results: A inverse significant correlation between TIT (mean 218.8 min ± 44.2) and troponin I levels in the period between day 0 and two days after HTX was observed. No influence of vasopressants on troponin I levels was noted. The weak trend towards ($r = 0.3$; $p = 0.17$) the positive correlation between donor's age and troponin I levels on the 1st day after HTX was observed. Similarly, the weak trend towards the positive correlation between stroke and higher troponin I levels on the 1st postoperative day ($p = 0.16$) was observed.

Conclusion: TIT does not correlate positively with increased troponin I values. The relationship demands further analysis. The donor's age and stroke as the cause of the donor's death

Streszczenie

Wstęp: Wybrane czynniki związane z dawcą serca mogą wpływać na stopień uszkodzenia pobranego od dawcy serca.

Cel pracy: Ocena wpływu wybranych czynników związanych z dawcą serca na wartości poziomów troponiny I w okresie okołoperacyjnym (od zerowej do trzeciej doby włącznie).

Materiał i metody: Analizą retrospektywną objęto 30 chorych (4 kobiety, 26 mężczyzn) w wieku 22–62 lat, średnio 48,5 ± 11,0. Badaną grupę stanowili pacjenci, których serca pobierane były wg identycznego schematu i u których zmierzono stężenia troponiny I w kolejnych dobach po transplantacji serca. Analizie poddano: wiek dawcy, przyczynę zgonu dawcy, rodzaj leków wspomagających układ krążenia dawcy, całkowity czas niedokrwienia. Oceniono wpływ wybranych parametrów na stężenie troponiny I w okresie okołoperacyjnym mierzonego metodą jednostopniowego testu immunoenzymatycznego (norma od 0,1 ng/ml).

Wyniki: Stwierdzono ujemną istotną statystycznie korelację pomiędzy całkowitym czasem niedokrwienia (średnio 218,8 min ± 44,2) a stężeniami troponiny I w okresie od zerowej do drugiej doby po transplantacji serca. Nie stwierdzono wpływu leków wazopresyjnych na stężenia troponiny I. Wykazano słabą tendencję ($r = 0,3$; $p = 0,17$) do dodatniej korelacji pomiędzy wiekiem dawcy serca a stężeniami troponiny I w pierwszej dobie po transplantacji serca. Podobnie wykazano słabą tendencję w zależności pomiędzy obecnością udaru mózgu a wyższymi wartościami stężeń troponiny I w pierwszej dobie ($p = 0,16$).

Wnioski: Całkowity czas niedokrwienia nie koreluje dodatnio ze wzrostem wartości troponiny I w pierwszych dobach po trans-

Address for correspondence: dr n. med. Karol Wierzbicki, Pradnicka Street 80, 31-202 Krakow, Poland, Tel. +48 12 614 30 75, +48 12 614 30 72, Fax +48 12 423 39 00, Email: lolekwierzbicki@onet.pl

can potentially influence higher troponin I levels (no statistical significance).

Key words: heart transplantation, troponin, donor's heart.

Introduction

Given the chronic lack of donors (in Poland and worldwide), development of surgical methods of the end stage heart failure treatment was observed [1].

However the proposed methods ("undersize" mitral anuloplasty, surgical ventricular reconstruction and others) did not obtain first class recommendation in the available guidelines. Despite lack of control studies, heart transplantation (HTX) is thought to significantly increase survival, exercise capacity, return to work, and quality of life compared with conventional treatment. According to ESC (European Society of Cardiology) guidelines, HTX gets the first class of recommendation with level of evidence C [2].

Half-life time in adult cardiac recipients currently exceeds 10 years. However perioperative mortality is still relatively high, rating 10-20%. The most frequent from all cause of death in that period is the primary graft failure (40%) [3].

Because of chronic lack of donors, more and more often organs from "marginal donors" must be accepted. According to ISHLT guidelines, ischemic time > 4 hours, donor age > 45 years or high doses of vasopressing agents are the factors predisposing to early graft failure [4].

Analysis of the transplanted heart injury markers in the early period after heart transplantation serves a purpose.

Troponin is built of actin filaments and is bound with tropomyosin C. It is functionally connected with contraction of skeletal and heart muscles. Structurally, troponin is a complex of three proteins.

Troponin I, which connects with actin and stabilizes troponin-tropomyosin complex, is a very sensitive, and nowadays, popular marker of cardiac damage. An increased troponin level not only points out to myocardial infarction (guidelines for the diagnosis of myocardial infarction) but is also observed during every myocardial damage (even if is relatively small). Moreover, troponin levels should correlate with the extent of myocardial damage, and repeated measurements allow for the observation of damage dynamics [5-7].

Measure of the extent of harvested heart injury may be the analysis of dynamics of troponin level changes in the particular periods after organ transplantation.

The hitherto papers have not presented explicit data concerning the role of troponin release after HTX and the influence of e.g. ischemic time on troponin levels, which justifies continuation of the studies [8-10].

Material and methods

30 patients (4 females, 26 males) were analyzed retrospectively, age: 22 to 62 years, average: 48.5 ±11.0. The study population consisted of the patients with the hearts harvested by the same surgeon (the first author) according to the same protection scheme using CELSIOR cardioplegic

plantacji serca. Istotna statystycznie ujemna korelacja wymaga dalszej analizy. Wpływ na wyższe wartości troponiny może mieć wiek dawcy oraz udar mózgu jako przyczyna zgonu dawcy.

Słowa kluczowe: przeszczep serca, troponina I, serce dawcy.

solution. All the patients had troponin I levels measured on the following days after HTX (when more than one value a day was present, the highest value of the day was used in the statistical analysis).

The following parameters were analysed: donor's age, cause of donor's death (stroke/trauma), use of vasopressive agents (dopamine/dobutamine, norepinephrine), total ischemic time (TIT). The influence of chosen parameters on troponin I levels in the perioperative period was assessed. Troponin I was measured using one-step immunoenzymatic method (normal values to 0.1 ng/ml).

Myocardial protection

CELSIOR, a widely accepted cardioplegic solution, was routinely used for donor heart protection in all the cases. The most important components of this solution, which enhanced the "protective power" are the following: mannitol, lactobionic acid, glutamic acid, histidine, calcium chloride, potassium chloride (15 mmol) and magnesium chloride. The solution is slightly alkaline (pH = 7.3), slightly hypertonic (242-368 mOsmol/L) with low viscosity (1.15 cSt), and has a high buffering capacity (acidic approximately 11 mmol, alkaline approximately 7 mmol).

During harvesting the donor heart was arrested with 2 liters of CELSIOR cardioplegic solution given directly into the aortic bulb. At the same time, the heart was topically cooled by the cold saline (NaCl 0.9%) solution with crashed ice. After excision of the heart, another, third liter of the CELSIOR solution was given into the aortic bulb. After the careful inspection of the explanted heart, and exclusion of the pathologies, the heart was placed in the same cardioplegic solution in at least 10 degrees Celsius to avoid freezing of the heart. The fourth liter of CELSIOR was infused directly before the implantation [11].

Statistical techniques

Statistical analysis was performed using STATISTICA 8.0 software. First, the type of the variables' distribution was assessed using basic statistical packages. Because all the analyzed parameters had the distribution distant from the normal one, non-parametric tests were used. Mann-Whitney and R Sperman tests were utilized. Results were described as arithmetic averages with statistical deviation. $p < 0.05$ was considered as statistically significant, $p < 0.2$ was considered as the weak trend.

Results

On the following days after HTX (from day 0 to day 3 after HTX) average troponin I levels were 20.4 ±13.8; 19.7 ±13.8; 15.6 ±14.1; 12.5 ±9.5, respectively.

There was an inverse correlation between TIT (mean 218.8 min \pm 44.2) and troponin I levels was noted in the period between day 0 and day 2 after HTX; $p < 0.05$ (on the 3rd day – weak trend; $r = -0.3$; $p = 0.16$) (R Sperman test) (Table I).

We have not found any influence of vasopressants (dopamine/dobutamine, norepinephrine) on troponin I levels (Mann–Whitney test) (Table II).

The weak trend ($r = 0.3$; $p = 0.17$) to positive correlation between donor's age (mean 33.9 \pm 13.9) and troponin I levels on the 1st day after HTX (R Sperman test) was observed (Table III).

A similar weak trend ($p = 0.16$) was observed in the correlation between stroke and higher levels of troponin I levels on the 1st day (Mann–Whitney test) (Table IV).

Discussion

Analysis of interdependence between troponin I levels and TIT on the consecutive days after HTX surprisingly showed the negative correlation. Data from the literature did not define the explicit correlation between TIT and troponin levels after HTX. Halwachs et al. did not find any correlation between TIT and troponin levels [9]. Similar lack of relationship was shown by Zimmermann et al. [10]. However, Ryan et al. in their experimental study noted a strong correlation between ischemic time and amount of troponin released after heart transplantation [8]. Also annual ISHLT registry points out to TIT as a risk factor for 1-year mortality [3]. Reverse correlation observed in our study (lower troponin levels observed during longer TIT) does not prove a “protective effect” of ischemic time prolongation, which seems obvious. One paper documented an unexpected higher risk of prima-

ry graft failure connected with very short ischemic time (in our study mean TIT = 218.8 min \pm 44.2, which was consistent with a generally accepted normal value of TIT < 4 hours) [12].

We aimed to examine the supplementary hypothesis: because longer ischemic time is often connected with prolonged reperfusion time (i.e. time from aortic declamping to stopping cardiopulmonary bypass), most probably longer reperfusion time may have had a “protective” effect and be the cause of lower troponin I levels in the patients with longer TIT. However, in our study group we did not find any significant correlation between TIT and reperfusion time ($r = -0.1$; $p = 0.5$) (additional data not shown in results). In our centre, reperfusion time in the patients after HTX dependent *de facto* on the moment when the transplanted heart starts to perform a hemodynamically effective function. An explanation of the reverse correlation between TIT and troponin values may be the acceptance of longer ischemic time, mainly due to low risk donors dedicated to “good” recipient (i.e. without pulmonary hypertension), which may limit perioperative graft injury but analysis of that hypothesis was not the purpose of our study [4, 9]. The described correlation requires further multivariate analysis on a greater material. At that stage we can only conclude about the lack of a direct risk of troponin level increase with TIT prolongation, with its average of less than 4 hours (mean 218.8 min \pm 44.2).

Statistical analysis showed the presence of a weak trend towards higher troponin I levels, when the cardiac donor's death was caused by stroke (in comparison with injury). Brain death is related with the two important stage factors my-

Tab. I. Analysis of the correlation between total ischemic time (TIT) and troponin I levels on the following days after HTX (trop0 – troponin I on day 0; trop1 – troponin I on day 1; trop2 – troponin I on day 2; trop3 – troponin I on day 3 after HTX) (R Sperman test)

	TIT (min)
Trop0	$p = 0.03^*$ $r = -0.4$
Trop1	$p = 0.03^*$ $r = -0.4$
Trop2	$p = 0.01^*$ $r = -0.5$
Trop3	$p = 0.16^{**}$ $r = -0.3$

*statistically significant reverse correlation; higher TIT correlates with lower values of trop0, trop1, trop2; **statistical trend; higher TIT correlates with lower trop3 values.

Tab. III. Analysis of interdependence between donor's age (D AGE) and troponin I levels on the following days after HTX (trop0 – troponin I day 0; trop1 – troponin I on day 1; trop2 – troponin I on day 2; trop3 – troponin I on day 3 after HTX) (R Sperman test)

	D AGE (years)
Trop0	$p = 0.52$ $r = 0.1$
Trop1	$p = 0.17^*$ $r = 0.3$
Trop2	$p = 0.36$ $r = 0.2$
Trop3	$p = 0.79$ $r = 0.1$

*statistical trend; higher donor's age correlates with higher trop1 levels.

Tab. II. Analysis of the interdependence between vasopressors' use in the donor (DM/DB – dopamine and/or dobutamine, NOR – norepinephrine, “+” – presence, “–” – absence) and troponin I levels after HTX (trop0 – troponin I on day 0; trop1 – troponin I on day 1; trop2 – troponin I on day 2; trop3 – troponin I on day 3 after HTX) (Mann–Whitney test)

	DM/DB + NOR +	DM/DB – DM/DB +	NOR + NOR –	DM/DB + NOR –
Trop0	$p = 0.46$	$p = 0.91$	$p = 0.32$	$p = 0.89$
Trop1	$p = 0.33$	$p = 0.70$	$p = 0.21$	$p = 1.0$
Trop2	$p = 0.96$	$p = 0.44$	$p = 0.54$	$p = 0.63$
Trop3	$p = 0.31$	$p = 0.84$	$p = 0.21$	$p = 0.57$

Tab. IV. Analysis of interdependence between donor's death cause (INJ – trauma, STR – stroke) and troponin I levels on the following days after HTX (trop0 – troponin I on day 0; trop1 – troponin I on day 1; trop2 – troponin I on day 2; trop3 – troponin I on day 3 after HTX) (Mann–Whitney test)

	INJ/STR
Trop0	$p = 0.41$
Trop1	$p = 0.16^*$
Trop2	$p = 0.22$
Trop3	$p = 0.46$

*statistical trend; STR is connected with higher trop1 level.

ocardial damage: 1. catecholamine storm causes vasoconstriction, tachycardia, which promotes myocardial ischemia, 2. urgent vasodilatation, which lowers coronary perfusion, augments myocardial ischemia. The mechanism of brain death may potentially influence the dynamics of the described processes [4]. However, ISHLT Registry data show no influence of the cause of death on 1-year mortality [3]. But as we know, stroke is often connected with arterial hypertension and uncontrolled hypertension leads to myocardial hypertrophy. Left ventricular hypertrophy of the donor may handicap graft protection and according to actual guidelines, it is an important risk factor for graft failure [4, 13].

The weak trend towards the higher troponin levels on the first day after HTX correlating with older donor's age was observed. Donor's age is a known risk factor for early graft failure. The obligatory guidelines recommend (class IIa) accepting donors aged up to 45 years, older donors could be accepted only under special additional conditions [3, 14].

In the presented material, the average donor's age was < 34 years, so it was the "safe age", which could result in the lack of the significant influence of donor's age on the extent of perioperative myocardial injury.

Also, vasopressor influence on the dynamics of troponin I levels after HTX was studied. Because of the logistic difficulties it was impossible to follow reliably the dosage of vasopressive agents that the heart donor was given (doses were modified many times during long-term infusion). So only the usage of selected drugs (dopamine/dobutamine, norepinephrine) on troponin levels after HTX was analysed. No relation of the mentioned drugs on troponin I values on the following days after HTX was noted. Although, it is known that high vasopressant doses may be the cause of early graft failure [15].

In our material, hearts demanding intensive pharmacological support were avoided. The decisions were made individually without any general scheme.

During analysis of troponin levels after HTX, a question about the influence of troponin values in the donor's heart can be asked. Reliable values of troponin in the heart donor were impossible to obtain due to technical problems (no measurement, no general scheme of troponin levels monitoring, different troponin types: I or T). Analysis by Khush et al. did not show any influence of elevated troponin levels in the heart donor on higher risk of recipient mortality or need for post-transplant mechanical circulatory support [16].

Study limitations:

- retrospective analysis based on archive data,
- limited number of the study group,
- limited number of analysed factors potentially influencing dynamics of troponin levels after HTX,
- impossibility of gaining reliable data concerning donor heart function after of the brain death,
- impossibility of univocal comparison of the literature data because of different types of troponin used (I or T),
- replacement of the previously used troponin I for highly sensitive troponin T (in 2010) in the authors' centre, which complicates prospective analysis.

Conclusion

TIT does not correlate positively with increasing troponin I levels on the first days after HTX. Statistically significant inverse correlation demands further analysis. The following factors may influence higher troponin levels: donor's age and stroke as the cause of death (weak trend).

The study was conducted upon the agreement of the Local Bioethical Committee (KBET/224/B/2010).

This work was supported by a grant from the Ministry of Science and Higher Education through the Jagiellonian University Medical College K/ZDS/002427

References

1. Sadowski J, Przybyłowski P, Wierzbicki K. Leczenie chirurgiczne niewydolności serca. W: Podolec P, Jankowska J, Ponikowski P. Przewlekła niewydolność serca. Wyd. 1. Medycyna Praktyczna, Kraków 2009, 469-481.
2. Dickstein K, Cohen-Solal A, Filippatos G, McMurray JJ, Ponikowski P, Poole-Wilson PA, Strömberg A, van Veldhuisen DJ, Atar D, Hoes AW, Keren A, Mebazaa A, Nieminen M, Priori SG, Swedberg K; ESC Committee for Practice Guidelines (CPG). ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM) Eur J Heart Fail 2008; 10: 933-989.
3. www.isHLT.org
4. Costanzo MR, Dipchand A, Starling R, Anderson A, Chan M, Desai S, Fedson S, Fisher P, Gonzales-Stawinski G, Martinelli L, McGiffin D, Smith J, Taylor D, Meiser B, Webber S, Baran D, Carboni M, Dengler T, Feldman D, Frigerio M, Kfoury A, Kim D, Kobashigawa J, Shullo M, Stehlik J, Teuteberg J, Ueber P, Zuckermann A, Hunt S, Burch M, Bhat G, Canter C, Chinnock R, Crespo-Leiro M, Delgado R, Dobbels F, Grady K, Kao W, Lamour J, Parry G, Patel J, Pini D, Towbin J, Wolfel G, Delgado D, Eisen H, Goldberg L, Hosenpud J, Johnson M, Keogh A, Lewis C, O'Connell J, Rogers J, Ross H, Russell S, Vanhaecke J; International Society of Heart and Lung Transplantation Guidelines. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. J Heart Lung Transplant 2010; 29: 914-956.
5. Solnica B. Badania laboratoryjne. W: Szczekliki A (red.). Choroby Wewnętrzne. Wyd. 2. Medycyna Praktyczna, Kraków 2010; 26-34.
6. Stępień E, Śnieżek-Maciejewska M, Szajna-Zych M, Sadowski J. Biochemiczne markery niedokrwienia mięśnia sercowego w diagnostyce zawału okołoperacyjnego uszkodzenia serca. Forum Kardiologów 2002; 7: 135-142.
7. Piątkowski R, Filipiak KJ, Zieliński A, Bobilewicz D, Opolski G. Troponiny w diagnostyce martwicy mięśnia sercowego. Terapia 2001; 111: 53.
8. Ryan JB, Hicks M, Cropper JR, Garlick SR, Kesteven SH, Wilson MK, Feneley MP, Macdonald PS. The initial rate of troponin I release post-reperfusion reflects the effectiveness of myocardial protection during cardiac allograft preservation. Eur J Cardiothorac Surg 2003; 23: 898-906.
9. Halwachs G, Iberer F, Pieber T, Müller H, Tscheliessnigg K, Tiran A, Sabin K, Wilders-Truschig M. Troponin T as a marker for posttransplantation adaptational problems of the donor heart. J Heart Lung Transplant 1996; 15: 451-455.
10. Zimmermann R, Baki S, Dengler TJ, Ring GH, Remppis A, Lange R, Hagl S, Kübler W, Katus HA. Troponin T release after heart transplantation. Br Heart J 1993; 69: 395-398.
11. Wierzbicki K, Sobczyk D, Milaniak I, Bochenek M, Piątek J, Drwiła R, Kapelak B, Krupa F, Przybyłowski P, Ciotczyk-Wierzbicka D, Sadowski J. Dynamika zmian stężeń troponiny I w pierwszych dobach po przeszczepieniu serca (HTX) w materiale własnym – pilot study. Kardiolog Torakochir Pol 2011; 8: 379-382.
12. Russo MJ, Iribarne A, Hong KN, Ramlawi B, Chen JM, Takayama H, Mancini DM, Naka Y. Factors associated with primary graft failure after heart transplantation. Transplantation 2010; 90: 444-450.
13. Januszewicz A, Prejbisz A. Nadciśnienie tętnicze. W: Szczekliki A (red.). Choroby Wewnętrzne. Wyd. 2. Medycyna Praktyczna, Kraków 2010; 335-350.
14. Young JB, Hauptman PJ, Naftel DC, Ewald G, Aaronson K, Dec GW, Taylor DO, Higgins R, Platt L, Kirklin J. Determinants of early graft failure following

cardiac transplantation, a 10-year, multi-institutional, multivariable analysis. *J Heart Lung Transplant* 2001; 20: 212.

15. Young JB, Naftel DC, Bourge RC, Kirklin JK, Clemson BS, Porter CB, Rodeheffer RJ, Kenzora JL. Matching the heart donor and heart transplant recipient. Clues for successful expansion of the donor pool: a multivariable, multiinstitutional report. The Cardiac Transplant Research Database Group. *J Heart Lung Transplant* 1994; 13: 353-364.
16. Khush KK, Menza RL, Babcock WD, Zaroff JG. Donor cardiac troponin I levels do not predict recipient survival after cardiac transplantation. *J Heart Lung Transplant* 2007; 26: 1048-1053.